REMARKS

Upon entry of the above claim amendments, Claims 1-4, 8 and 9 are pending in the present application.

Claims 1-4 are instantly amended to more clearly define the subject matter that Applicants deem to be their invention. More specifically, the term "solvate, or solvate of a salt" has been deleted from the claims, without prejudice.

Claim 8 is instantly amended to correct minor informalities.

No new matter has been added.

Reconsideration and withdrawal of the objections and the rejections of the present application in view of the remarks herewith, is respectfully requested, as the application is in condition for allowance.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-4 and 8-9 have been rejected under 35 U.S.C. 112, First Paragraph, as allegedly failing to comply with the specification, while being enabling for compounds of formula (I) and (IA) and salts thereof, does not reasonably provide enablement for solvates or solvates of salts of compounds of formula (I) or (IA). Applicants strongly disagree.

Nevertheless, without conceding the validity of the Examiner's allegation and solely for facilitating the prosecution of the present application, the afore-mentioned claims have been amended to recite compounds of formula (I) and (IA) and salts thereof. Accordingly, the rejections under 35 U.S.C. § 112, First Paragraph, are now moot. Therefore, reconsideration and withdrawal of the rejections of the afore-mentioned claims under 35 U.S.C. § 112, First Paragraph is respectfully requested.

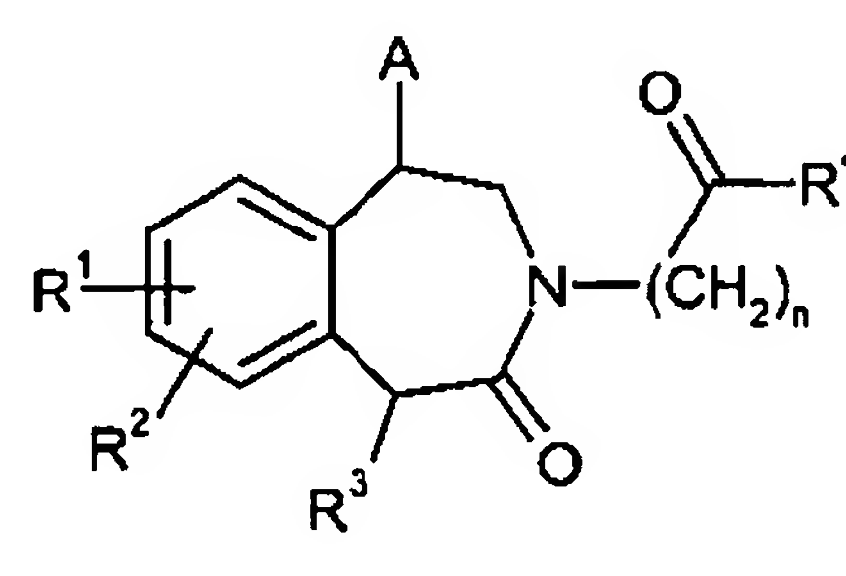
Rejections under 35 U.S.C. § 103 (a)

Claims 1-4 and 8-9 have been rejected under 35 U.S.C. 103(a), as allegedly being unpatentable over Hamanaka et al. (WO 97/48701; hereinafter "Hamanaka") in view of Pandit et al. (Journal of Biological Chemistry, Vol. 275(39), 2000, 30610-30617; hereinafter "Pandit"). The Examiner asserted that compounds of Hamanaka are structural isomers of the presently claimed

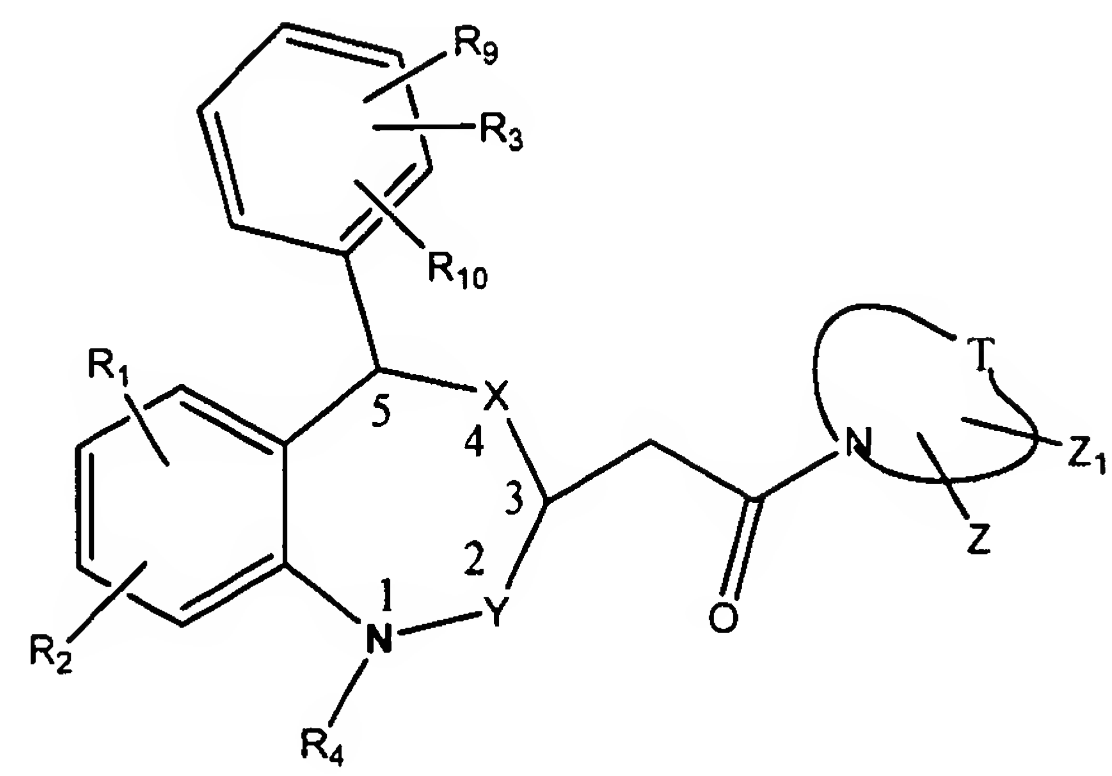
compounds and that the Hamanaka compounds and the presently claimed compounds are three-dimensionally similar (*See* Page 10 of the Action). The Examiner further alleged that it was obvious to people skilled in the art to reach the presently claimed compounds by modifying the Hamanaka compounds in view of Pandit's teaching on the crystal structure of human squalene synthase. Applicants respectfully traverse.

To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills,* 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.,* 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.,* 299 F.3d 1313, 1333-34 (Fed. Cir. 2002). The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

The present invention is directed to a compound of Formula (I) as follows:



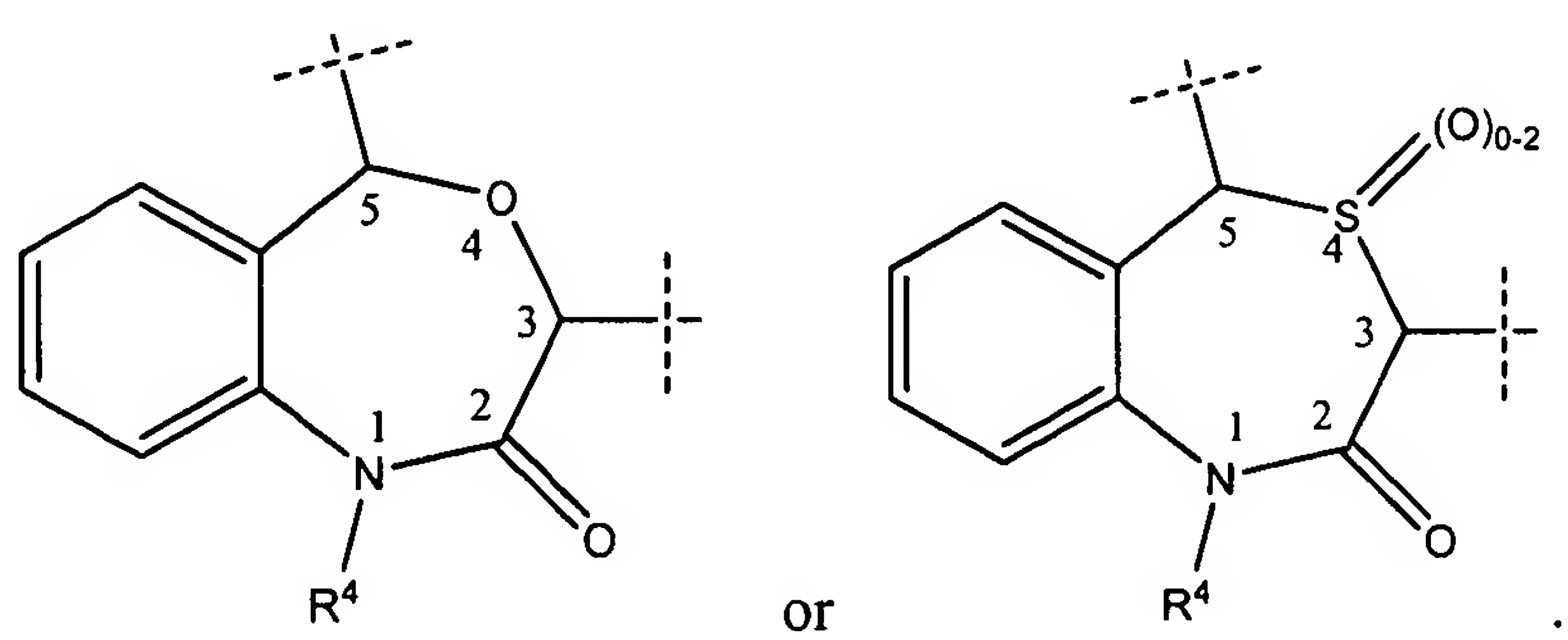
or a salt. All the variables are defined in the present application. In contrast, Hamanaka discloses a compound of the following formula:



wherein R^1, R^2, R^3, R^4, R^9, R^{10}, X, Y, T, Z, and Z_1 are defined therein (*see* page 3 of Hamanaka). Applicants note that X in Hamanaka is oxy, thio, -S(O)- or $-S(O)_2$-.

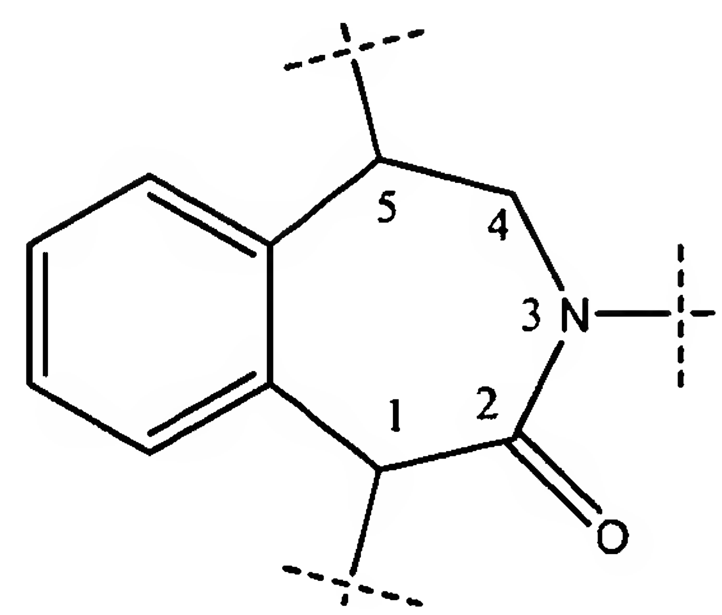
Applicants respectfully assert that the compounds of the present invention and the Hamanaka compounds are fundamentally distinct. More specifically, the presently claimed compounds and the Hamanaka compounds differ in at least at three positions (position 1, 3 and 4) of the "core" 7-membered ring.

Hamanaka discloses the derivatives of 4,1-benzoxazepine or 4,1-benzothiazepine with core structures as follows:



In Hamanaka's formula, the 4-position of the "core" 7-membered ring is O, or $S(=O)_{0\text{-}2}$; the 3-position is carbon; and the 1-position is nitrogen.

In contrast, the compounds of the present invention are benzo[d]azepin-2-one derivatives with the following core structure:



As above demonstrated, the 4-position of the "core" 7-membered ring of the presently claimed compounds is carbon; the 3-position is nitrogen; and the 1-position is carbon. In view of these differences, Applicants respectfully assert that one of ordinary skill in the art would not readily consider the presently claimed compounds and the Hamanaka compounds as structural isomers.

Further, Applicants submit that even one of these differences, let alone all three differences in the core structure, is sufficient to make the Hamanaka compounds and the presently claimed compounds patentably distinct.

For example, in the instances when the Hamanaka compounds have oxygen or sulfide at the 4-position of the 7-membered rings, the compounds are in cyclo-ether or cyclo-thioether type of structures. It is well known in the art that the chemical properties of cyclo-ether or cyclo-thioethers are distinct from the corresponding cycloalkyl compounds. For example, it is well understood in the art that the presence of two lone pairs of electrons on the oxygen (or sulfide) atoms makes hydrogen bonding with water molecules possible, that ethers can act as Lewis bases, and that ethers can complex with a Grinard reagent to stablize the reagent in solution (*see* L.G. Wade, Organic Chemistry, 3rd Edition, 1995, Prentice-Hall, Inc., pp. 595-597). As such, one of ordinary skill in the art would not have be motivated to replace O or S with carbon in a compound's core structure. Even assuming, *in arguendo,* that one were to make such a modification, there would have been no reasonable expectation of success in the art that the same/similar properties would be obtained once

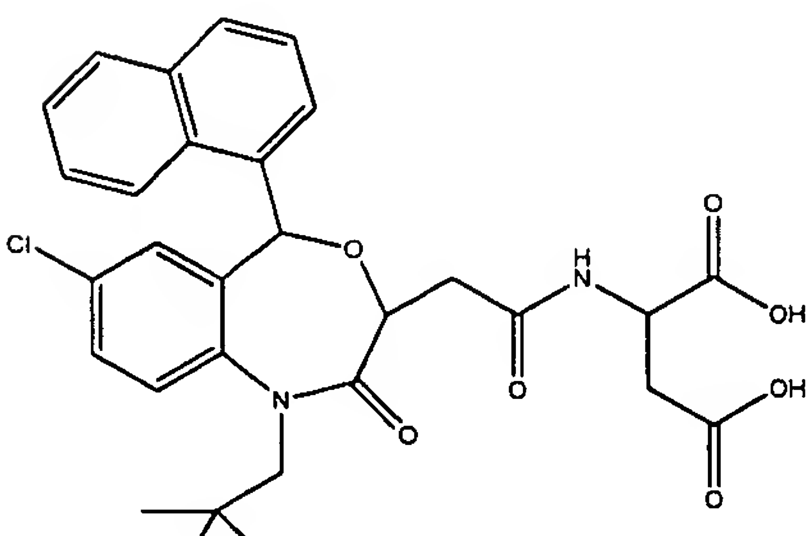
an ether or thioether compound (in Hamanaka) is modified to have a carbon instead(as directed in the present invention).

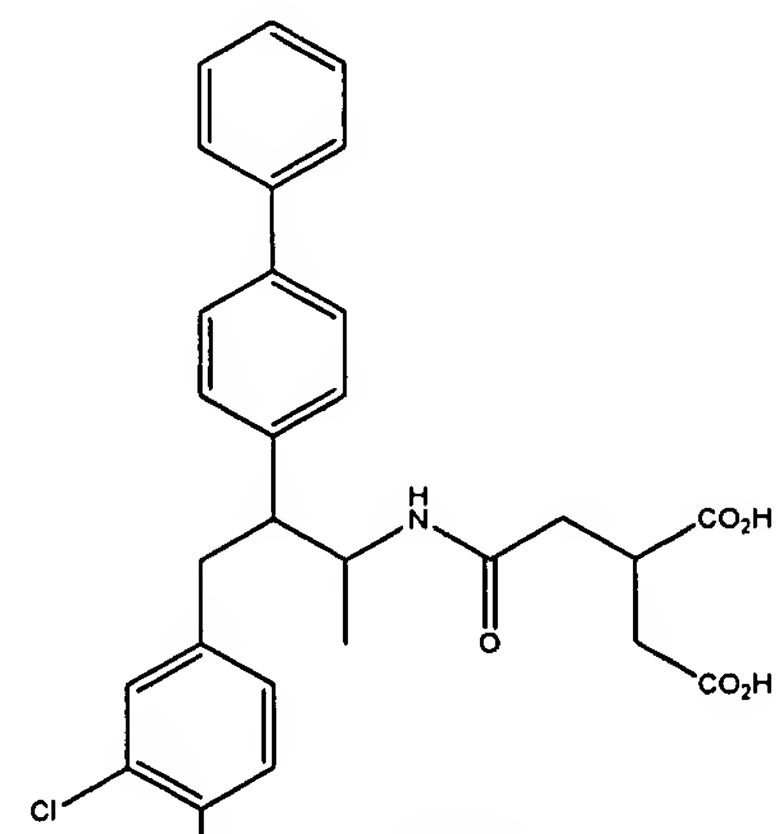
Also, for the instances when X is -S(O)- or $-S(O)_2$- at the 4-position in Hamanaka (i.e. sulfoxide and sulfone compounds), the chemical properties of these compounds are distinct from those having carbon at that position (as directed by the present invention). For example, it is well known that energy barriers for inversion are high for sulfoxides at its sulfur center and thus chiral sulfoxides can be used in asymmetric synthesis; also, sulphones can react with a variety of electrophiles to form the corresponding substituted sulphones due to their ability to stabilize α-carbanions; further, a sulphone group can be easily removed from a compound's structure (*see* attached Exhibit A). In contrast, the corresponding alkyl compounds are not associated with these properties. As such, one of ordinary skill in the art would expect that compounds with sulfoxide and sulfone moieties have different properties than those having alkyl moieties in place.

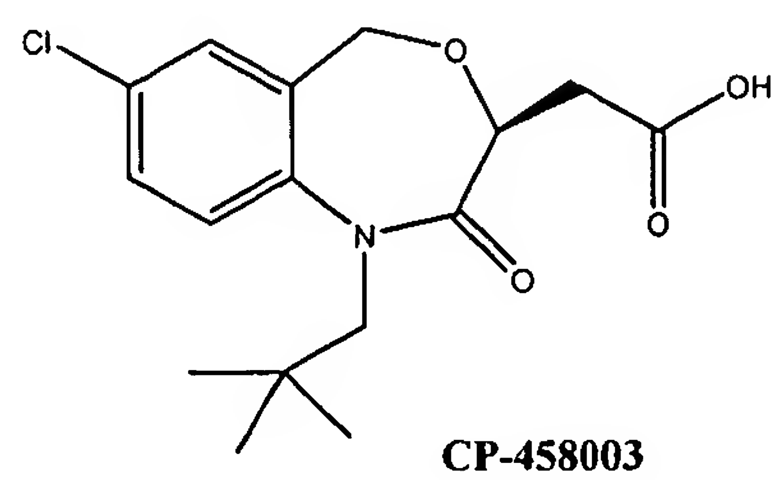
In addition, Applicants note that that the Examiner has not provided any reference to support the assertion that the Hamanaka compounds and the presently claimed compounds are three-dimensionally similar. Applicants respectfully disagree with this assertion. For example, it is within common knowledge of the art that C-C bond is a neutral bond, while O-C is a polar bond. Accordingly, a skilled artisan would expect that the 7-membered rings in Hamanaka and the present invention differ conformationally at least at the 4-position. Similarly, the 7-membered rings shall also differ conformationally at their 1 and 3-positions. Even if the compounds bear similar functionality off certain positions of the 7-membered ring, the spatial position of those functionalities would likely be very different in light of the differences to the "core" ring. Indeed, even the slightest change in three dimensional conformation could drastically alter the pharmacological properties of the compounds. As such, one of ordinary skill in the art would expect that the Hamanaka compounds and the presently claimed compounds are conformationally dissimilar.

At least for the above reasons, the compounds of the present invention are not obvious in view of Hamanaka. Applicants also note that Hamanaka does not provide any motivation or suggestion to modify the compounds therein to arrive at those recited in the present invention.

Further, Applicants respectfully submit that Pandit fails to cure the deficiencies of Hamanaka. Pandit teaches three compounds, CP-320473, CP-424677 and CP-458003, as possible human squalene synthase inhibitors. The Pandit compounds have chemical structures as follows:


CP-320473


CP-424677


CP-458003

Pandit does not teach or suggest a compound having a carbon atom at 4-position of its 7-membered ring (as directed by the present invention). Nor does Pandit teach or suggest any compound having a nitrogen at the 3-position and/or a carbon at 1-position of its 7-membered ring.

Furthermore, Pandit reports that IC_{50} values against human squalene synthase for CP-320473, CP-424677 and CP-458003 are 56 nM, 32 nM and 30 μM respectively. The best inhibitor identified by Pandit is CP-424677, which has no 7-membered ring system in its structure. Meanwhile, Pandit reports that CP-458003 (a compound with a 7-membered ring) is <u>a thousand fold less active</u> than CP-424677. In view of Pandit's disclosure, one skilled in the art would not reasonably expect that the 7-membered ring is essential to a compound's inhibitory activity against human squalene synthase.

Indeed, Pandit only teaches that bulky hydrophobic groups (napthyl group in CP-320473 and biphenyl group in CP-424677) are good for potency (See p. 30614 of Pandit). When applicable, these groups actually appear off the corresponding 5-position of the 7-membered ring in the presently claimed compounds and the Hamanaka compounds. Pandit does not teach or suggest any modification at the 4-position of its 7-membered ring, not even to mention modifications at the 1-, 3-, and 4- postions altogether. Clearly, Pandit fails to provide the much-needed motivation or suggestion for modifying the Hamanaka compounds to arrive at the present invention.

In summary, Applicants respectfully submit that: first, neither Hamanaka nor Pandit teaches or suggests compounds of the present invention; second, there is absolutely no teaching or motivation in Hamanaka and/or Pandit to modify their compounds to reach the present invention; third, there is no justifiable expectation for success to arrive at the present invention by modifying Hamanaka compounds in view of Pandit's disclosure.

At least of the reasons above discussed, the present invention is patentable over Hamanaka in view of Pandit. Therefore, the rejections under 35 U.S.C. 103(a) are improper and respectfully traversed.

CONCLUSION

In view of the amendments and remarks made herein, the present application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105 under Order No. 81927 (303989).

Date: December 22, 2008

Customer number
21874

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Selected Aspects of Organosulphur Chemistry

Reading and Literature References

Advanced Organic Chemistry, *Part B*, Carey and Sundberg, 3rd Ed., Plenum.
Organosulphur Chemistry, Whitham, Oxford.
Organic Chemistry, Clayden, Greeves, Warren and Wothers, Oxford.

Key-Concepts and Compound Classes

Sulphones, sulphuranes, sulphides, sulphonic acids, sulphonamides, thioacetals, thiocarbonyl compounds, thiols.

Name Reactions

Questions

Sulphur

Sulphur is a p-block element in Group VI and is located immediately below oxygen in the periodic table. Sulphur is less electronegative than oxygen, possessing electronegativity characteristics comparable to carbon. Sulphur forms sufficiently strong bonds with carbon such that the compounds can be isolated, however, these linkages are weak enough to be efficiently and selectively cleaved in the presence of much stronger carbon-oxygen bonds. Sulphur also forms stable bonds to itself, with crystalline elemental sulphur being comprised of eight membered rings.

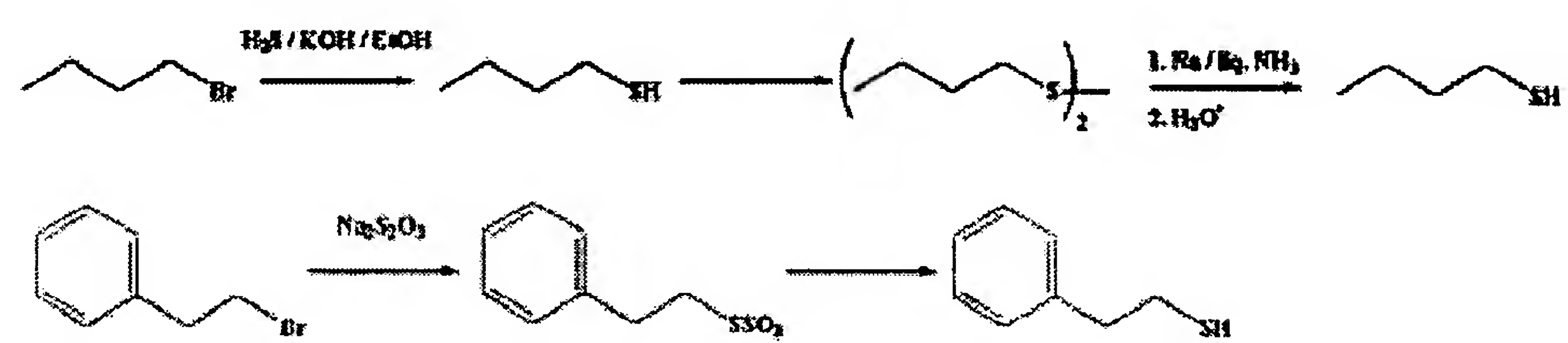
Bond Strength (kJ mol^{-1})				
X =	C	H	F	S
C–X	376	418	452	362
S–				

X	362	349	384	301

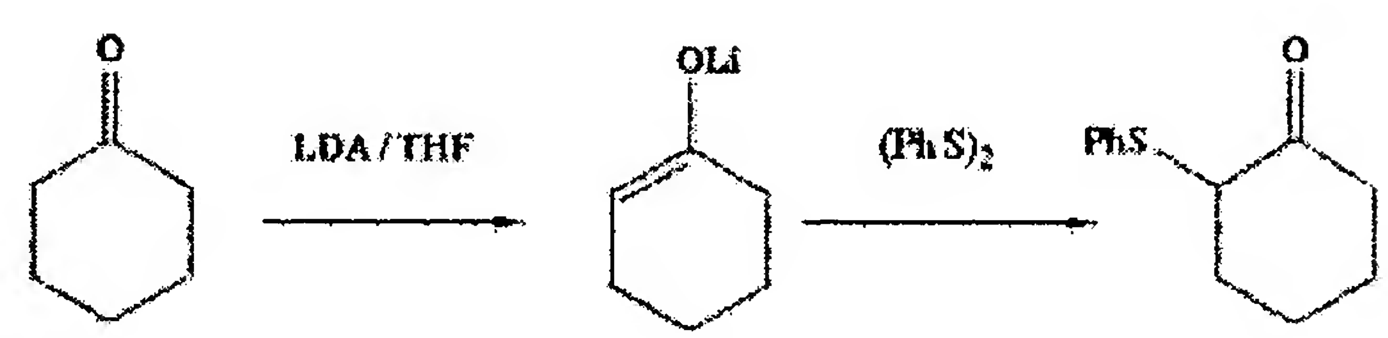
Sulphur is an extremely versatile element, it can exist in a variety of oxidation states (+II, +IV and + VI) and it can behave in both an electrophilic and nucleophilic manner. For example, divalent (S(II)) compounds are good nucelophiles, possessing high energy non-bonding lone pairs ($3sp^3$ c.f. $2sp^3$ for oxygen). Different names are in use to describe classes of organosulphur compounds. The table below lists some of the most commonly used terms.

Thiols

Aliphatic thiols are typically prepared *via* nucleophilic displacement of aliphatic halides with reagents such as H_2S, KS.CS.OEt or $Na_2S_2O_3$. The initial thiol product is susceptible to further alkylation that can lead to sulphide formation (*via* the H_2S route) and therefore 'protected' or masked sulphur derivatives are used to avoid this side reaction (i.e. KS.CS.Oet or $Na_2S_2O_3$).

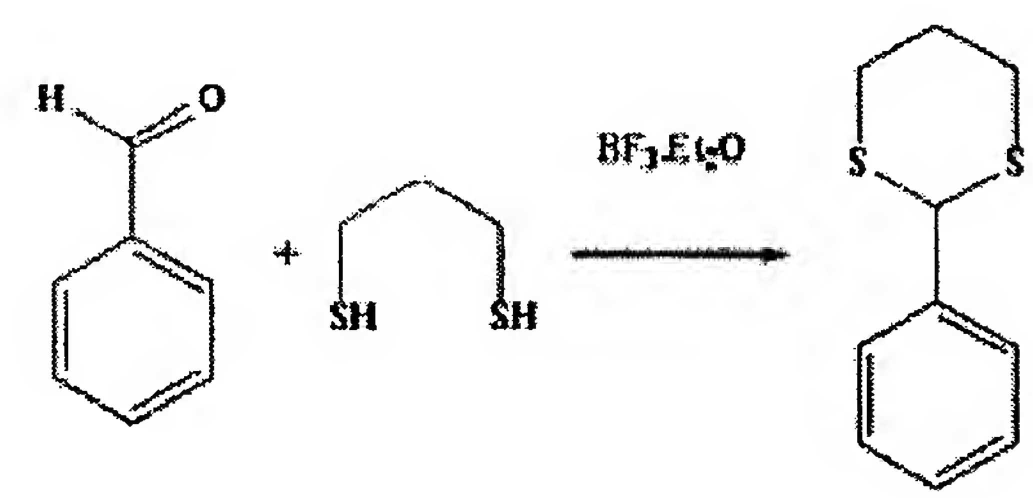


In contrast, aromatic thiols are typically produced by reduction of sulphonyl halides, which in turn are produced by direct chlorosulphonylation of the aromatic substrate. Alternatives to this route include treatment of aromatic lithium species with elemental sulphur. Similarly, reaction of lithium enolates with disulphides (S-S bond) leads to sulphides as shown below.

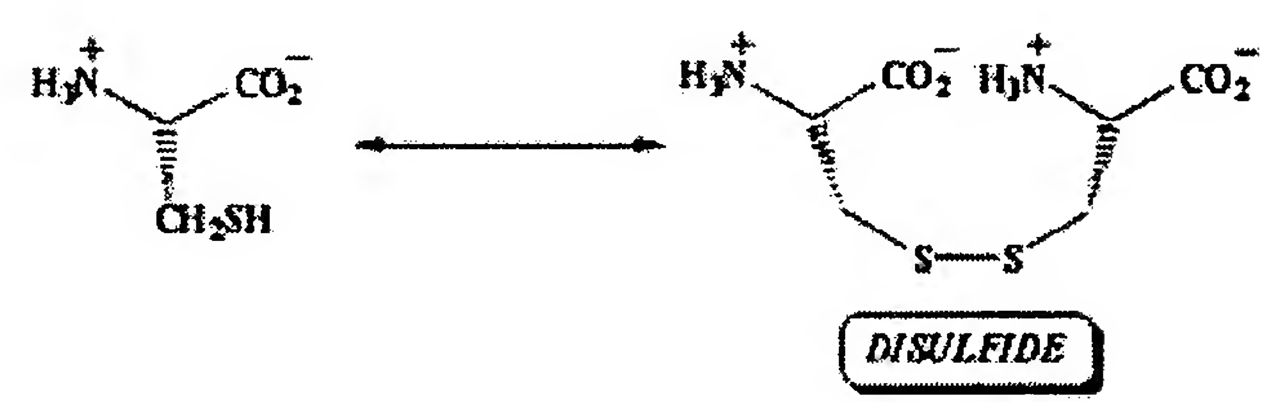


Thiols are more acidic than alcohols (pK_a for EtSH ~10.5 c.f. EtOH ~16; PhSH ~6.5, PhOH ~10.0) and this difference can be accounted for the aromatic thiol/phenol pair by less effective resonance stabilisation in the RS^- form (involving 3p-2p overlap) *c.f.* RO^- (involving 2p-2p overlap). Therefore thiols are easily deprotonated under mild basic conditions (alkali hydroxides/alkoxides). In addition, sulphur possesses a very high affinity for metals such as

mercury or silver and stables salts with these metals are easily formed. (*Thiols are also known as '**mercaptans**' as a direct result of their ability to capture mercury*). Sulphur compounds are better nucleophiles than oxygen compounds towards saturated carbon atoms *via* S_N2 type reactions. Thiols are used frequently in combination with aldehydes and ketones to form dithioacetals (in effect masking the carbonyl group from alternative reaction pathways). Dithioacetal formation is favourable (it is an equilibrium reaction) as a direct result of the enhanced nucleophilicity of the sulphur centre.

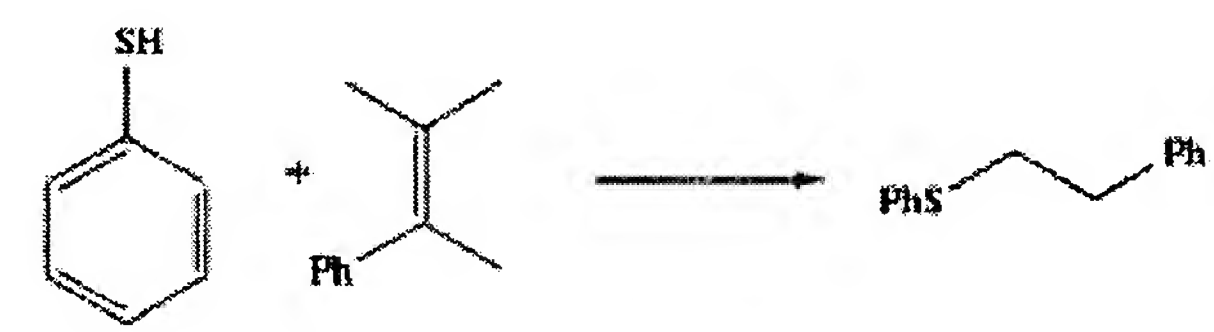


Thiol-disulphide interconversion in an extremely important process in natural systems, often responsible for the complex architecture of peptides and proteins and their resultant biological functions. For example, the amino acid cysteine can readily dimerise to form cystine linkages. When peptide sequences possess more than two cysteine residues, determination of the exact structure of the biologically active species is difficult. In cases where the free thiol form of the peptide/protein is the active species, biochemists will add a slight excess of a water soluble thiol to prevent cystine cyclisation phenomena.



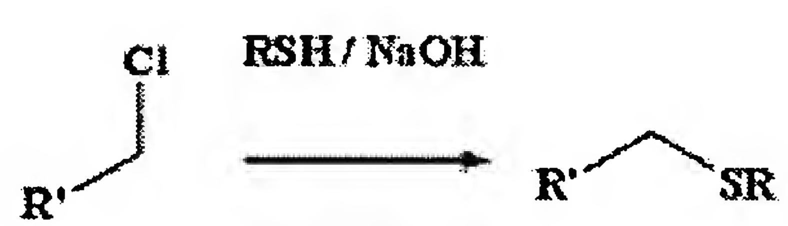
Thiols exhibit the tendency to behave as hydrogen donors in free radical reactions as a direct consequence of the weak S–H bond (364 kJ mol^{-1} *c.f.* 435 kJ mol^{-1} for O–H). This type of reaction is exothermic in nature and requires a low activation energy and thus thiols are frequently employed in mechanistic studies as radical traps.

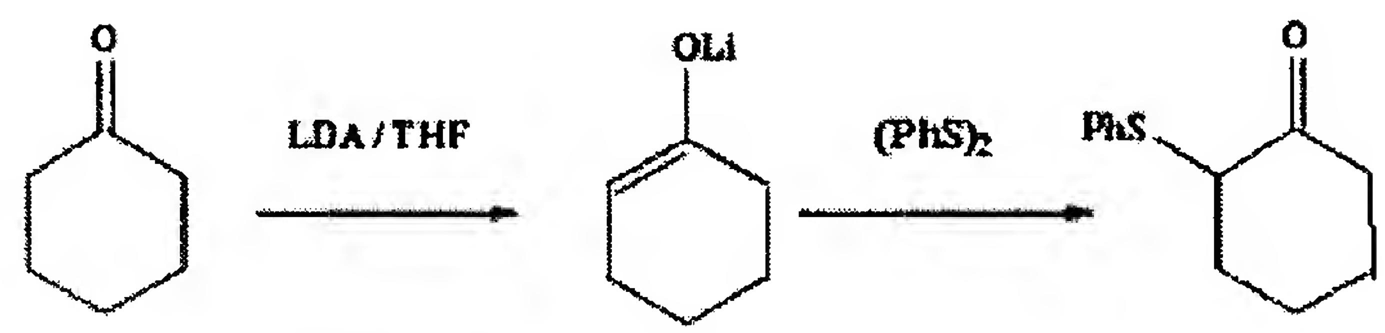
For example, following activation of alkenes *via* photochemical means, thiols can be used to reduce alkenes in a regiospecific manner (i.e. the thio-radical undergoing addition at the less substituted end of the double bond).



Sulphides (Thioethers)

Sulphides are also referred to a *thioethers* and are readily constructed by use of thiols attacknh electrophilic carbon centres in a nucleophilic manner. However, sulphur can also act as an *electrophilic* species and thus substitution reactions involving nucleophilic carbon, for example formation of a-phenylthiocycolhexanone.

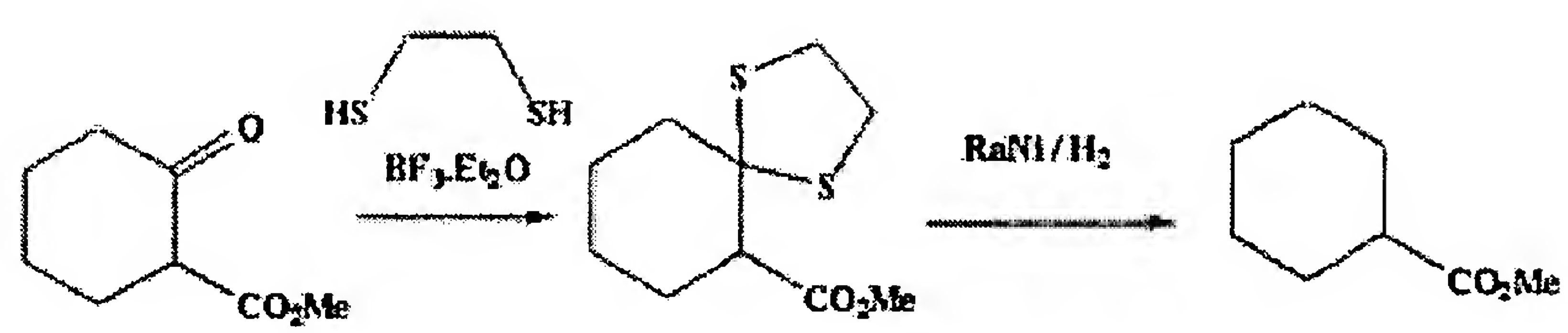




Other electrophilic sulphur sources such as PhSCl or $PhSSO_2Ph$ can also be employed.

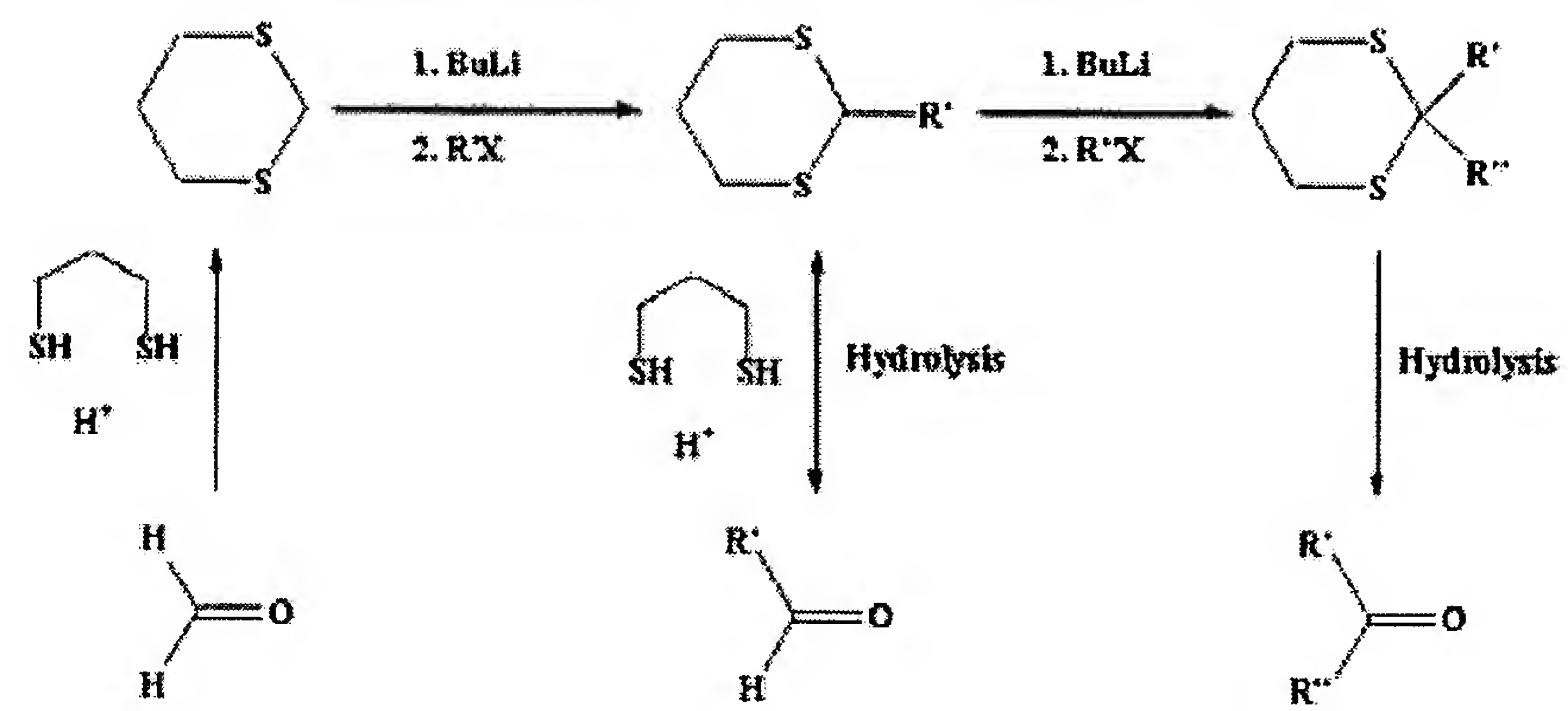
Thioacetals

Thioacetals can be produced by addition of a thiol or dithiol to either aldehydes or ketones and the thioacetals that result can act as effective protecting groups for these carbonyl systems. Thioacetals are reduced by Raney Nickel to afford the corresponding alkane. In addition it is possible to cleave selectively one of the C-S bonds using Cohen's radical anion methodolgy, enabling the preparation of a-metallated sulphides.



Arguably the most important use of thioacetals is the metallation of simple aldehyde

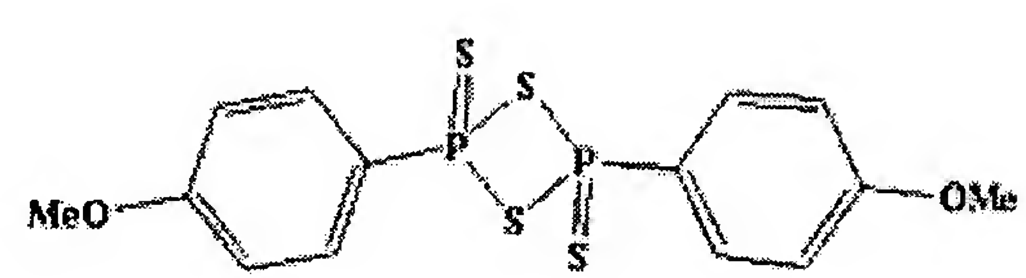
dithioacetals. Sulphur possesses the ability to ***stabilise a-carbanions*** and it follows that two sulphur atoms located a- to a carbanion should enhance this effect. Corey and Seebach discovered that 1,3-dithianes could be easily metallated using BuLi in dry THF. Subsequent treatment of the lithiated dithiane species with a wide range of electrophiles resulted in the production of derivatised aldehydes (from formaldehyde) and ketones following hydrolysis of the dithiane. In summary, formaldehyde can be converted to a higher order aldehyde or even through to the fully alkylated ketone. Upon metallation, the carbon atom that was orginally the electrophilic carbonyl centre has become nucleophilic in character in the 1,3-dithiane. This is referred to as ***Umpolung*** (reversal of polarity).



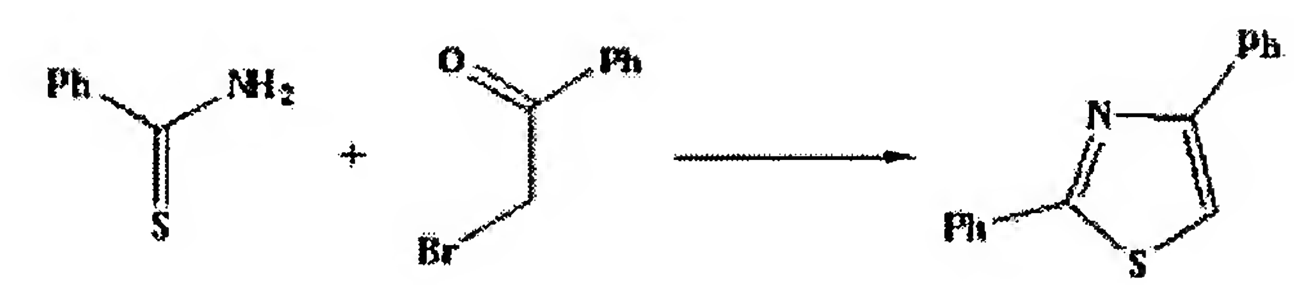
This sequence allows the preparation of otherwise not readily available aldehydes.

Thiocarbonyl Compounds

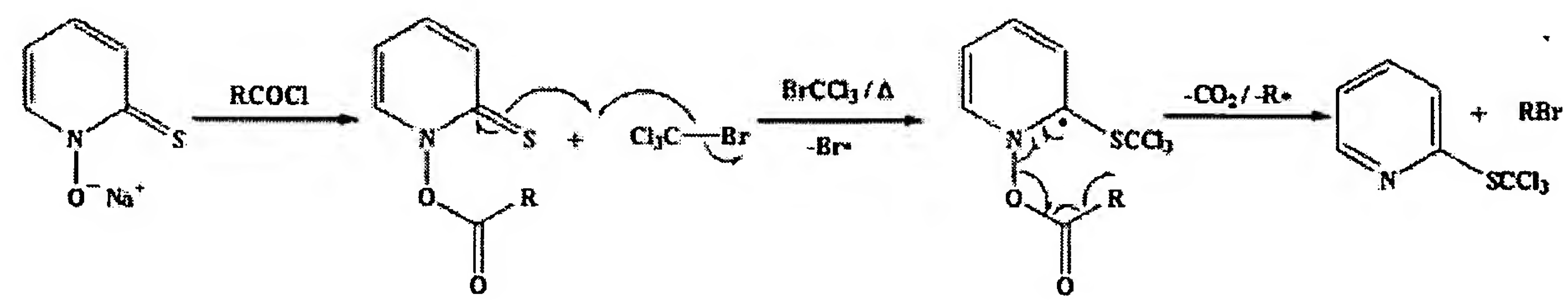
Multiple bonding to adjacent carbon is considerably more effective for oxygen (2p-2p, p-bonding) than in the case for sulphur (3p-2p, p-bonding) and this carbonyl compounds are far more stable than the corresponding thiocarbonyl derivatives. Thus, simple thioaldehydes and thioketones are not very stable and tend to trimerise. Increased stabilisation of thiocarbonyl systems is observed as greater resonance stabilisation can occur through electron release mechanisms and thus thioamides are far more stable than aliphatic thioketones. A general approach to the synthesis of thiocarbonyl systems is direct thionation of the carbonyl analogues – thus heating with phosphorous sulphides (such as P_2S_5) was used. Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetane-2,4-disulphide) is now more commonly employed with the thionation proceeding *via* a mechanism similar to the Wittig reaction involving a 4-membered cyclic intermediate.



Thioamides are quite stable compounds and the chemistry of these systems is relatively specialised. A general theme throughout their chemistries is alkylation at sulphur as shown below in the Hantzsch synthesis of thiazoles:



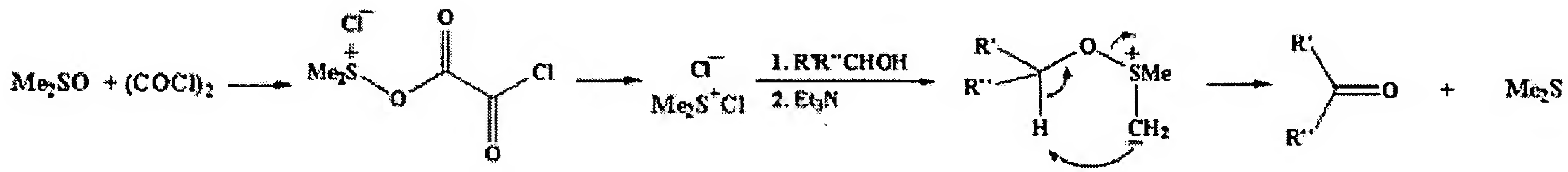
A thiocarbonyl derivative was used by Barton in an efficient method for the production of alkyl radicals from carboxylic acid derivatives. The reaction is based upon ***thiophilic*** radical attack onto sulphur. In the case shown below, a carboxylic acid derivative is converted into the corresponding halide and is thus a modified Hunsdiecker reaction.



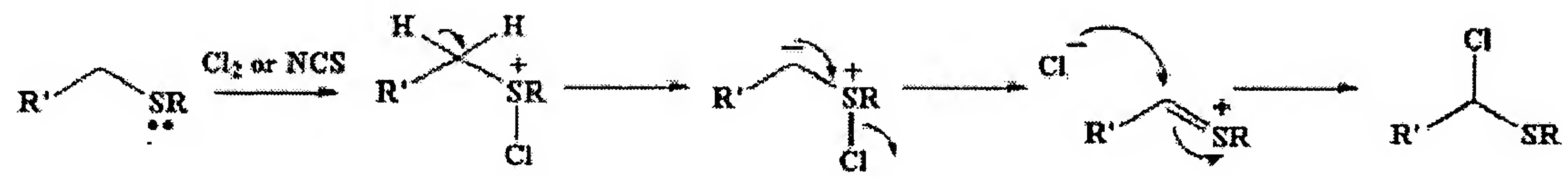
Sulphoxides

Sulphoxides are perhaps one of the most important classes of organosulphur compounds – they are easily prepared and readily converted into more complex organosulphur species. Dimethyl sulphoxide (**DMSO**) is a widely used dipolar aprotic solvent and also a key precursor to a range of useful reagents. Sulphoxides possess pyramidal configurations at the sulphur centre and optically active sulphoxides (R'R"SO) are well known. Inversion barriers are quite high in the case of simple alkyl or aryl sulphoxides and thus racemisation only occurs above 200 °C and thus chiral sulphoxides have been used in asymmetric synthesis. Sulphoxides are typically produced by oxidation of the corresponding sulphide (using aqueous hydrogen peroxide) and care must be taken to prevent exhaustive oxidation through the sulphone. Sodium periodate in aqueous methanol at 0 °C is employed to selectively produce the desired sulphoxide.

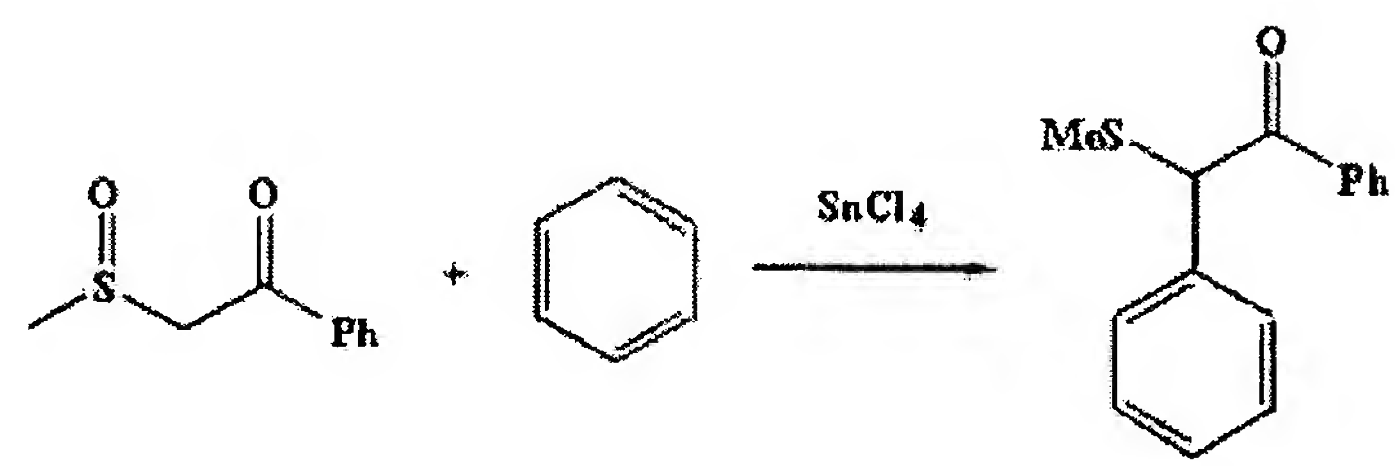
The Swern Oxidation is a very mild oxidation procedure that employs DMSO and oxalyl chloride to convert either primary or secondary alcohols into the corresponding carbonyl species. The first step involves reaction between oxalyl chloride and DMSO at −78 °C to afford chlorosulphonium chloride. Subsequent reaction with the alcohol affords an alkoxysulphonium salt. This derivative collapses *via* an ylide intermediateto form the desired carbonyl species and dimethyl sulphide.



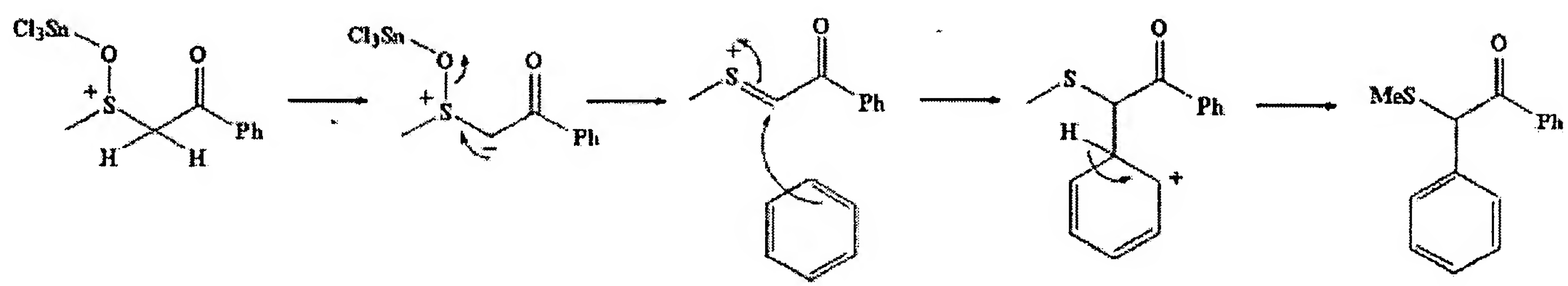
The Pummerer Rearrangement is a useful method to generate α-substituted sulphides.



The are many variations of this rearrangement and treatment of sulphoxides with anion-stabilising substituents to encourage ylide formation generates cations that are extremely reactive – for example cations of this type may even react with nucleophiles such as aromatic derivatives. In these cases, Lewis acids are frequently used to remove the oxygen from the sulphoxide. The sulphur atom stabilises the cation thus formed to counteract the destabilisation by ketones (as shown below) and the Lewis acid is employed to ensure that there cannot be any competitive nucleophilic reaction with benzene.

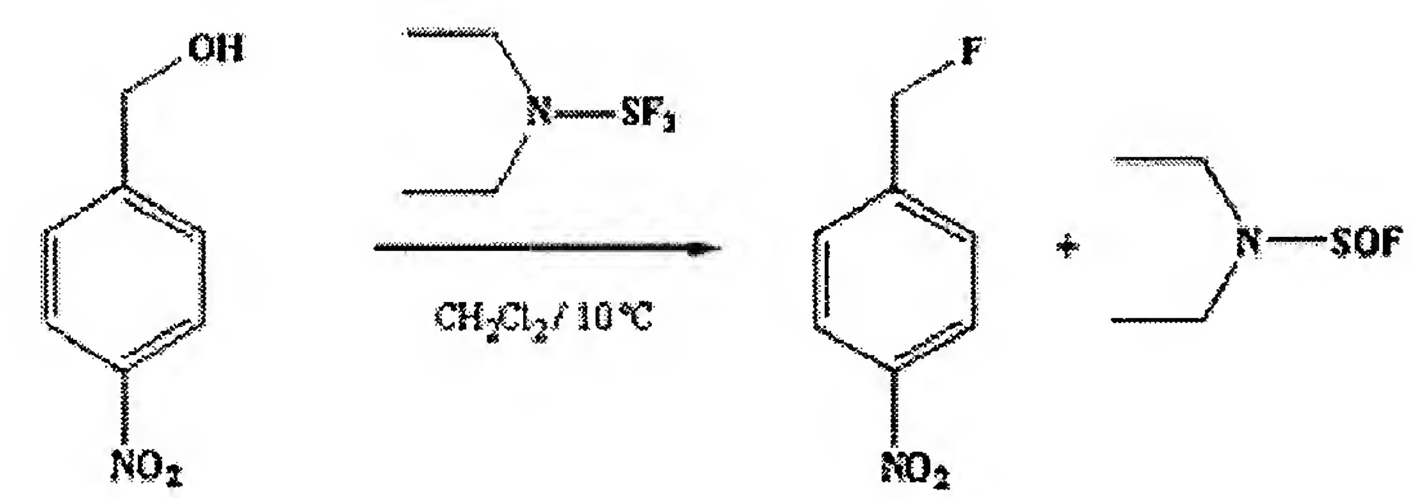


Mechanism



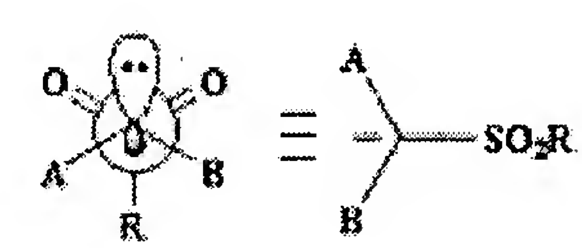
Sulphuranes

Sulphuranes are extremely reactive species. Thus, sulphur tetrafluoride is a powerful fluorinating agent. Due to its reactivity it is extremely difficult to handle. Diethylaminosulphurtrifluoride (DAST) has been developed as an alternative to sulphur tetrafluoride and is easier to use. This commercially available reagent is obtained by the reaction of diethyltrimethylsilyl amine with sulphur tetrafluoride and can be utilised to convert the hydroxyl groups of primary, secondary and tertiary alcohols and the oxygen atoms of carbonyl groups of aldehydes and ketones to fluorine.

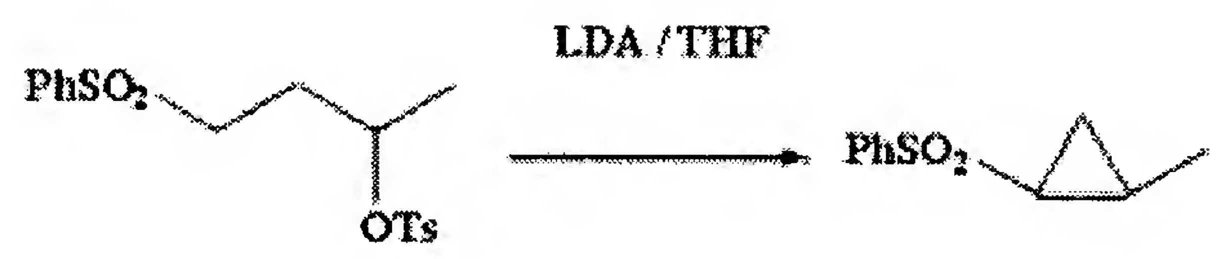


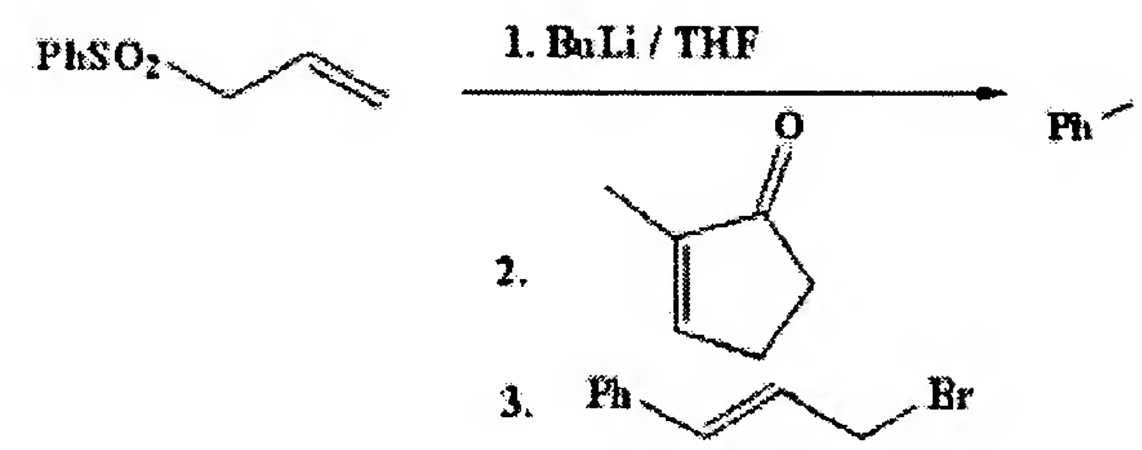
Sulphones

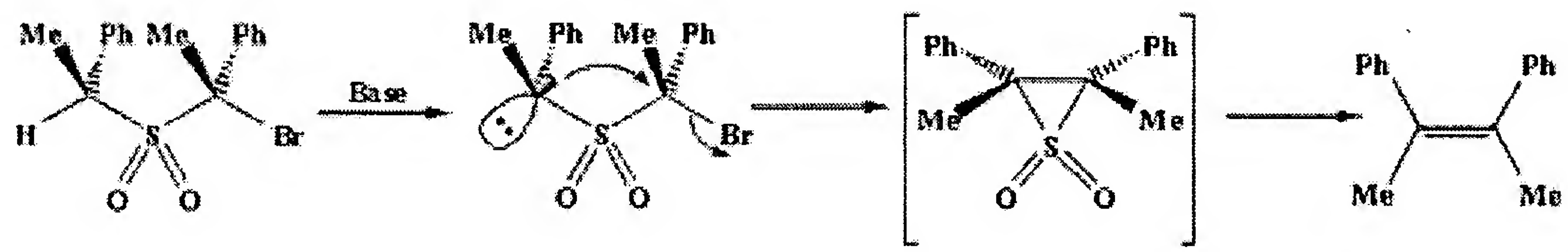
Sulphones are of great synthetic interest and these typically crystalline compounds find extensive use in organic chemistry. Sulphones can be prepared by Friedel-Crafts procedures using Lewis acids and sulphonyl halides, although the fluorosulphone precursors are required for efficient conversion. Sulphones can also be prepared by oxidation of sulphides and sulphoxides. Sulphones find most use in synthetic chemisty as a result of their ability to stabilise a-carbanions and to thus react with a variety of electrophiles to form the corresponding substituted sulphones. The model proposed to account for the enhanced stability of the a-carbanions of sulphones is shown below where the lone pair of electrons is gauche to the two S=O bonds and with the a-carbanion adopting a pyramidal configuration. The two substituents can participate in resonance stabilisation and the SO^2 group stabilises the carbanion *via* ***inductive*** and **not** resonance effects.



α-Sulphonyl carbanions can be obtained by treatment of the sulphone with BuLi or LDA in dry THF. Quenching with a diverse set of electrophiles can then occur and a few examples are shown below:



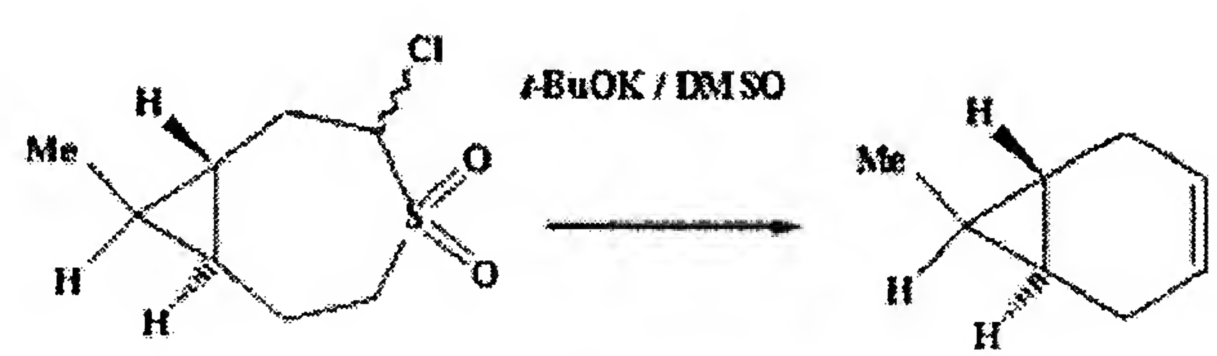




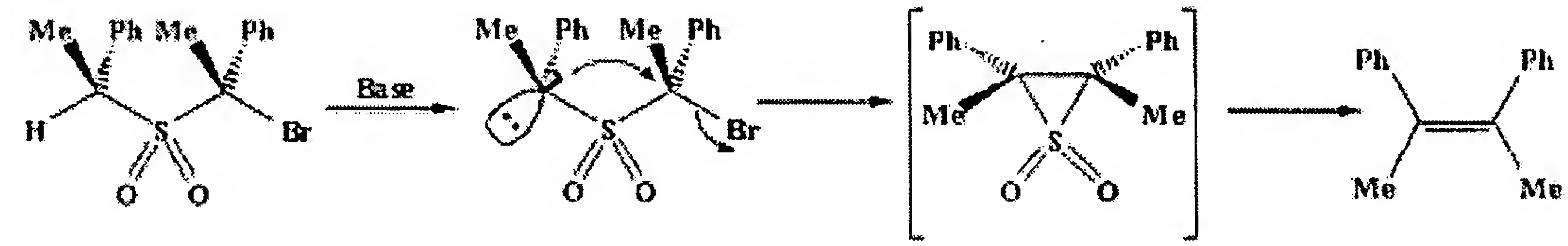
An example of a 'Tandem' Micheal Addition

In order for sulphones to be generally applicable in organic synthesis, it is necessary that that the sulphone group, having served as a stabilising influence during carbon-carbon bond formation, be easily removed following the synthetic manipulation step. A few key examples of this type of reaction sequence are highlighted below:

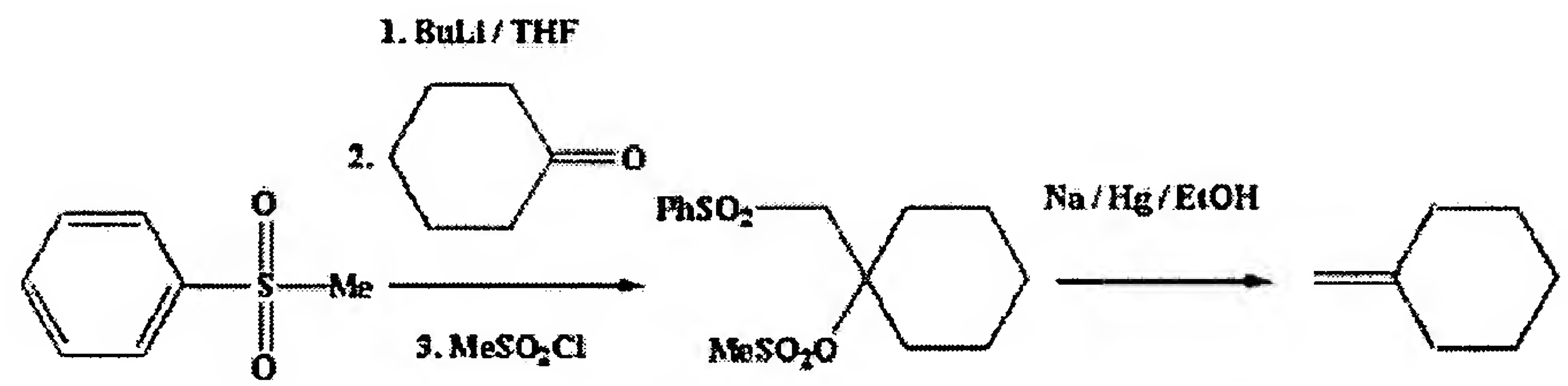
The Ramberg-Backlund Reaction: α-Halosulphones undergo an intramolecular cyclisation following carbanion formation to form unstable thiirane dioxides (or known as *episulphones*). The thiirane dioxide thus formed rapidly decomposes to generate the corresponding alkene and sulphur dioxide.



The Julia Reaction is a stereoselective method for the synthesis alkenes by reduction of ß-hydroxyarylsulphones. Theß-hydroxyarylsulphone is first converted into either the acetate, benzoate or sulphonate derivative and this derivative is then treated with sodium amalgam to afford the corresponding alkene *via* reductive elimination.

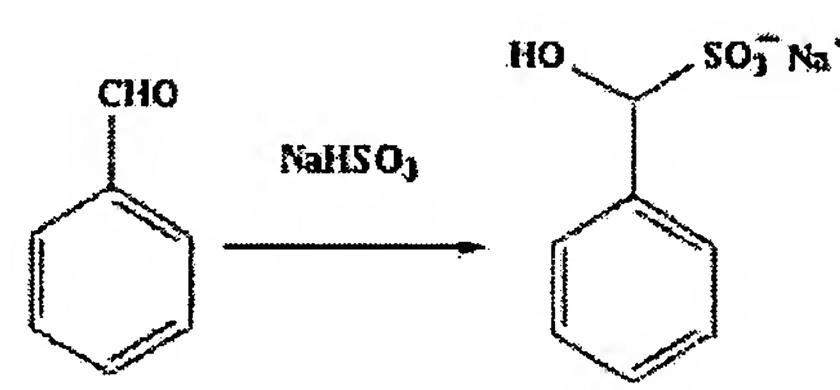


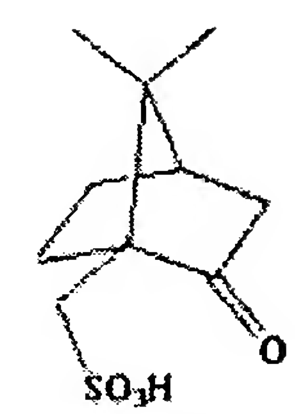
The stereoselectivity observed in this process is a key feature. The alkene formation involves overall electron addition to the arenesulphonyl group and loss of an arenesulphinate ion. Subsequent β-elimination of the leaving group occurs from the carbanion then occurs, although this carbanion is sufficiently long-lived to enable equilibration of the pyramidal anions to occur so as to favour formation of *E*-alkenes. Steric factors of the sulphone substituents also plays a role, and with larger groups enhanced *E*:*Z* ratios are observed. As a result of the relatively mild conditions that are employed, the Julia reaction has been used extensively in natural product synthesis, especially in cases where two complex substrates need to be coupled together *via* an *E*-double bond.



Sulphonic Acids and Derivatives

Sulphonic acids can be prepared *via* several methods including direct sulphonation using concentrated sulphuric acid or sulphur trioxide or substitution or addition reactions involving sulphite ions as the nucleophilic species.





(+)-(1S)-10-Camphorsulfonic Acid

Sulphonic acids are very strong organic acids, possessing comparable pK_a values to sulphuric acids. Since these acids exhibit excellent solubility characteristics in common organic solvents, they are frequently employed as acid catalysts for reactions in aprotic solvents. In addition, they are non-oxidising and unlike acids such as HCl, their conjugate bases are very poor

nucleophiles. Camphorsulphonic acid (CSA) is frequently used as an acid catalysts. Sulphonic acids are readily converted into the corresponding ester, amides and halide derivatives. These derivatives are of great synthetic utility, for example sulphonate esters are used as excellent leaving groups in nucleophilic substitution reactions ith the tosylates, mesylates or triflates being very popular. Of these leaving groups, triflates are themost reactive, exhibiting reactivities $>10^4$ in typical S_N1 and S_N2 reactions.

Sulphonamides are used to protect amines as they are extremely stable amine derivatives and have also been found to exhibit useful biological acitivity (see the arthritis drug ***Feldene*** manufactured by Pfizer). Simple sulphonamides are formed by treatment of the amine with the sulphonyl halide. Sulphonamide formation has been used (in the form of the Hinsberg test) to identify the nature of the amine species. This is a direct result of the effect of the sulphonyl group upon the adjacent amide group - sulphonamide groups are acidic (p*Ka* ~ 10-11). Thus, treatment of primary, secondary and tertiary amines will afford corresponding primary, secondary and tertiary sulphonamides that exhibit very different reactivity and solubility characteristics. Primary sulphonamides are soluble in aqueous alkali, whereas secondary sulphonamides are not soluble in alkaline aqueous media. Tertiary amines do not react with sulphonyl halides. An example of the use of sulphonamides is shown below in the synthesis of an aza-macrocycle.

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